Table 1 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified degradation product	—	0.10
Total degradation products	—	0.5

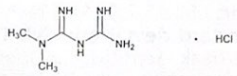
[a] Process impurity, included for peak identification only; monitored in the drug substance.

[b] 3-Benzyl-5-[(3,5-dimethylphenoxy)methyl]oxazolidin-2-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers. Store at controlled room temperature.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Metaxalone RS
  USP Metaxalone Related Compound B RS
  1-Amino-3-(3,5-dimethylphenoxy)propan-2-ol.
  $C_{11}H_{17}NO_2$ 195.26
  USP Metaxalone Related Compound C RS
  Bis[2-hydroxy-3-(3,5-dimethylphenoxy)propyl]amine.
  $C_{22}H_{31}NO_4$ 373.49

Metformin Hydrochloride



$C_4H_{11}N_5 \cdot HCl$ 165.62

Imidodicarbonimidic diamide, *N*,*N*-dimethyl-, monohydrochloride;
1,1-Dimethylbiguanide monohydrochloride [1115-70-4].

DEFINITION

Metformin Hydrochloride contains NLT 98.5% and NMT 101.0% of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B. IDENTIFICATION TESTS—GENERAL,** *Chloride* ⟨191⟩: Meets the requirements

ASSAY

- **PROCEDURE**
  Sample: 60 mg of Metformin Hydrochloride
  Analysis
  [NOTE—To avoid overheating of the reaction medium, mix thoroughly throughout the titration, and stop the titration immediately after the endpoint has been reached.]
  Dissolve the *Sample* in 4 mL of anhydrous formic acid, and add 50 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 8.28 mg of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).
  Acceptance criteria: 98.5%–101.0% on the dried basis

IMPURITIES

- **RESIDUE ON IGNITION** ⟨281⟩: NMT 0.1%

Delete the following:

- **HEAVY METALS,** *Method I* ⟨231⟩: NMT 10 ppm (Official 1-Jan-2018)
- **ORGANIC IMPURITIES**
  Mobile phase: 17 g/L of monobasic ammonium phosphate in water, adjusted with phosphoric acid to a pH of 3.0
  System suitability stock solution: 0.25 mg/mL of metformin hydrochloride and 0.1 mg/mL of melamine in water
  System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.
  Standard stock solution: 0.2 mg/mL of USP Metformin Related Compound A RS in water
  Standard solution: 0.001 mg/mL of USP Metformin Related Compound A RS in *Mobile phase* from the *Standard stock solution*
  Sample solution: 5 mg/mL of Metformin Hydrochloride in *Mobile phase*
  Diluted sample solution: 0.005 mg/mL of Metformin Hydrochloride in *Mobile phase* from the *Sample solution*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 218 nm
  Column: 4.6-mm × 25-cm; packing L9
  Flow rate: 1.0–1.7 mL/min
  Run time: NLT twice the retention time of metformin
  Injection volume: 20 µL
  System suitability
  Sample: *System suitability solution*
  Suitability requirements
  Resolution: NLT 10 between melamine and metformin
  Analysis
  Samples: *Standard solution*, *Sample solution*, and *Diluted sample solution*
  Calculate the percentage of metformin related compound A in the portion of Metformin Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of metformin related compound A from the *Sample solution*
r_S = peak response of metformin related compound A from the *Standard solution*
C_S = concentration of USP Metformin Related Compound A RS in the *Standard solution* (mg/mL)
C_U = concentration of Metformin Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other impurity in the portion of Metformin Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times D \times 100$$

r_U = peak response of an individual impurity from the *Sample solution*
r_S = peak response of metformin from the *Diluted sample solution*
D = dilution factor for the preparation of the *Diluted sample solution*, 0.001

Acceptance criteria
Individual impurities: NMT 0.02% for metformin related compound A; NMT 0.1% for any other impurity

USP Monographs

Total impurities: NMT 0.5%

SPECIFIC TESTS

- **LOSS ON DRYING ⟨731⟩**
  Analysis: Dry a sample at 105° for 5 h.
  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**
  USP Metformin Hydrochloride RS
  USP Metformin Related Compound A RS
  1-Cyanoguanidine.
  $C_2H_4N_4$ 84.08

Metformin Hydrochloride Tablets

DEFINITION

Metformin Hydrochloride Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

- **A. INFRARED ABSORPTION ⟨197K⟩**
  Sample: Transfer an amount of powdered Tablets, equivalent to 20 mg of metformin hydrochloride, to a suitable flask. Add 20 mL of dehydrated alcohol, and shake. Filter, evaporate the filtrate on a water bath to dryness, and dry the residue at 105° for 2 h.
  Acceptance criteria: Meet the requirements
- **B.**
  Solution A: Dissolve 1 g of 1-naphthol in a solution containing 6 g of sodium hydroxide and 16 g of anhydrous sodium carbonate in 100 mL of water.
  Sample solution: Triturate an amount of powdered Tablets, equivalent of 50 mg of metformin hydrochloride, with 10 mL of water, filter, and use the filtrate.
  Analysis: To 5 mL of the *Sample solution* add 1.5 mL of 5 N sodium hydroxide solution and 1 mL of *Solution A*. Add 0.5 mL of sodium hypochlorite TS, dropwise, and with shaking.
  Acceptance criteria: An orange-red color is produced that darkens on standing.
- **C. IDENTIFICATION TESTS—GENERAL,** *Chloride* **⟨191⟩**
  Sample solution: Prepare as directed for the *Sample solution* in *Identification* test *B*.
  Acceptance criteria: Meet the requirements

ASSAY

- **PROCEDURE**
  Standard solution: 10 µg/mL of USP Metformin Hydrochloride RS in water
  Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer the amount of powder, equivalent to 100 mg of metformin hydrochloride, to a 100-mL volumetric flask. Add 70 mL of water, shake by mechanical means for 15 min, dilute with water to volume, and filter, discarding the first 20 mL of the filtrate. Dilute 10.0 mL of the filtrate with water to 100.0 mL, and dilute 10.0 mL of the resulting solution with water to 100.0 mL. The nominal concentration of this solution is 10 µg/mL.
  Instrumental conditions
  (See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
  Mode: UV
  Analytical wavelength: Wavelength of maximum absorbance at about 232 nm
  Cell: 1 cm
  Blank: Water
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of the Tablets taken:

$$\text{Result} = (A_U/A_S) \times (C_S/C_U) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

- **DISSOLUTION ⟨711⟩**
  Test 1
  Medium: pH 6.8 phosphate buffer; 1000 mL
  Apparatus 1: 100 rpm
  Time: 45 min
  Standard solution: USP Metformin Hydrochloride RS in *Medium*
  Sample solution: Pass a portion of the solution under test through a suitable filter.
  Instrumental conditions
  (See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
  Mode: UV
  Analytical wavelength: Wavelength of maximum absorbance at about 233 nm
  Analysis: Determine the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by using UV absorption of filtered portions of the *Sample solution*, suitably diluted with *Medium*, if necessary, in comparison with the *Standard solution*.
  Tolerances: NLT 70% (*Q*) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.
  Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
  For products labeled to contain 500 mg of metformin hydrochloride
  Medium: pH 6.8 phosphate buffer; 1000 mL
  Apparatus 2: 50 rpm
  Time: 30 min
  Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.
  Tolerances: NLT 80% (*Q*) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.
  For products labeled to contain 850 or 1000 mg of metformin hydrochloride
  Medium: pH 6.8 phosphate buffer; 1000 mL
  Apparatus 2: 75 rpm
  Time: 30 min
  Standard solution, Sample solution, Instrumental conditions, and **Analysis:** Proceed as directed in *Test 1*.
  Tolerances: NLT 75% (*Q*) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.
  Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.
  Medium: pH 6.8 phosphate buffer; 1000 mL
  Apparatus 1: 100 rpm
  Time: 60 min
  Buffer: Dissolve 1.38 g of monobasic sodium phosphate in about 1800 mL of water. Add 3.484 g of 1-pentanesulfonic acid sodium salt. Adjust with diluted phosphoric acid to a pH of 3.00 ± 0.05. Dilute with water to 2000 mL.

Mobile phase: Acetonitrile and *Buffer* (1:19)
Standard stock solution: 0.25 mg/mL of USP Metformin Hydrochloride RS in *Medium*. Use sonication to dissolve.
Standard solution: 0.05 mg/mL of USP Metformin Hydrochloride RS in *Medium* from the *Standard stock solution*
Sample solution: Pass a portion of the solution under test through a nylon filter of 0.45-µm pore size. Dilute with *Medium*, if necessary, to obtain a solution with a concentration similar to that of the *Standard solution*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.0 mL/min
Injection volume: 40 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Column efficiency: NLT 1500 theoretical plates
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times (V/D) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 1000 mL
D = dilution factor of the *Sample solution*

Tolerances: NLT 70% (Q) of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) is dissolved.

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **Organic Impurities**

Mobile phase: 17 g/L of monobasic ammonium phosphate in water, adjusted with phosphoric acid to a pH of 3.0
System suitability stock solution: 0.25 mg/mL of metformin hydrochloride and 0.1 mg/mL of melamine in water
System suitability solution: Transfer 1.0 mL of the *System suitability stock solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.
Sample solution: Weigh and finely powder NLT 20 Tablets. Transfer the amount of powder, equivalent to 500 mg of metformin hydrochloride, to a 100-mL volumetric flask. Dissolve in *Mobile phase* with shaking, dilute with *Mobile phase* to volume, and filter.
Diluted sample solution: Nominally 0.005 mg/mL of metformin hydrochloride in *Mobile phase* from the *Sample solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 218 nm
Column: 4.6-mm × 25-cm; packing L9
Flow rate: 1.0–1.7 mL/min
Run time: NLT twice the retention time of metformin
Injection volume: 20 µL
System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 10 between melamine and metformin
Analysis
Samples: *Sample solution* and *Diluted sample solution*
Calculate the percentage of any individual impurity in the portion of the Tablets taken:

$$\text{Result} = (r_U/r_S) \times D \times 100$$

r_U = peak response of any individual impurity from the *Sample solution*
r_S = peak response of metformin from the *Diluted sample solution*
D = dilution factor for the preparation of the *Diluted sample solution*, 0.001

Acceptance criteria
Any individual impurity: NMT 0.1%
Total impurities: NMT 0.6%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩
USP Metformin Hydrochloride RS

Metformin Hydrochloride Extended-Release Tablets

DEFINITION

Metformin Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

IDENTIFICATION

- **A.** The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Buffer solution: 0.5 g/L of sodium 1-heptanesulfonate and 0.5 g/L of sodium chloride in water. Before final dilution, adjust with 0.06 M phosphoric acid to a pH of 3.85.
Mobile phase: Acetonitrile and *Buffer solution* (1:9). [Note—To improve the separation, the composition of acetonitrile and *Buffer solution* may be changed to 1:19, if necessary.]
Diluent: 1.25% solution of acetonitrile in water
Standard solution: (L/4000) mg/mL of USP Metformin Hydrochloride RS in *Diluent*, where L is the labeled quantity, in mg, of metformin hydrochloride in each Tablet
System suitability stock solution: 12.5 µg/mL each of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent*
System suitability solution: Dilute 0.5 mL of the *System suitability stock solution* with the *Standard solution* to 50 mL.
Sample stock solution: Finely powder NLT 10 Tablets. Transfer powder, equivalent to the average Tablet weight, to a homogenization vessel, and add 500 mL of a 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized. [Note—A suggested homogenization sequence is as follows. Homogenize the sample using five pulses, each of 5 s, at about 20,000 rpm, and allow to soak for 2 min. Repeat these steps two additional times.]
Sample solution: Pass a portion of the *Sample stock solution* through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate. Transfer 25 mL of

the filtrate to a 200-mL volumetric flask, and dilute with water to volume.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 218 nm
Column: 3.9-mm × 30-cm; 10-µm packing L1
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 10 µL
Run time: Until after the elution locus of metformin related compound C

System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for metformin related compound B, metformin, and metformin related compound C are 0.86, 1.0, and 2.1–2.3, respectively. Metformin related compound C can have a variable retention time. The composition of the *Mobile phase* may be changed to 1:19, if it elutes at a relative retention time of less than 2.1.]

Suitability requirements
Resolution: NLT 1.5 between the peaks due to metformin related compound B and metformin
Tailing factor: NLT 0.8 and NMT 2.0 for the metformin peak
Relative standard deviation: NMT 1.5% for the metformin peak and NMT 10% for each of the peaks due to metformin related compound B and metformin related compound C

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Metformin Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of metformin hydrochloride in the *Sample solution*

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **DISSOLUTION** ⟨711⟩

Test 1
Medium: pH 6.8 phosphate buffer solution; 1000 mL
Apparatus 1: 100 rpm for Tablets labeled to contain 750 mg
Apparatus 2: 100 rpm for Tablets labeled to contain 500 mg
Times: 1, 3, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable hydrophilic polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration similar to that of the *Standard solution*.
Analysis: Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) released at each time point:

$$\text{Result} = [(A_U/A_S) \times C_S \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S)] \times (100/L)$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
V = initial volume of *Medium* in the vessel (mL)
V_S = volume withdrawn from the vessel for previous samplings (mL)
C_{60} = concentration of metformin hydrochloride in *Medium* determined at 1 h (mg/mL)
C_{180} = concentration of metformin hydrochloride in *Medium* determined at 3 h (mg/mL)
L = label claim (mg/Tablet)

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved, 500-mg Tablet (%)	Amount Dissolved, 750-mg Tablet (%)
1	20–40	22–42
3	45–65	49–69
10	NLT 85	NLT 85

The percentages of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Prepare as directed for *Test 1*; 1000 mL.
Apparatus 2: 100 rpm
Times: 1, 2, 6, and 10 h
Detector: UV 232 nm
Standard solution: USP Metformin Hydrochloride RS in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable polyethylene filter of 0.45-µm pore size. Dilute, if necessary, with *Medium* to a concentration that is similar to that of the *Standard solution*.
Analysis: Calculate, in mg/mL, the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in *Medium* at each time point, t:

$$\text{Result} = (A_U \times C_S \times D_U)/A_S$$

A_U = absorbance of the *Sample solution*
C_S = concentration of metformin hydrochloride in the *Standard solution* (mg/mL)
D_U = dilution factor of the solution under test
A_S = absorbance of the *Standard solution*

Calculate the percentage of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at each time point by the following formulas.
Percentage dissolved at the first time point (1 h):

$$\text{Result} = (C_1 \times V \times 100)/L$$

C_1 = content of metformin hydrochloride in *Medium* at the first time interval (mg/mL)
V = volume of *Medium*, 1000 mL
L = label claim (mg/Tablet)

Percentage dissolved at the second time point (2 h):

$$\text{Result} = [C_2 \times (V - SV_1) + C_1 \times SV_1] \times (100/L)$$

C_2 = content of metformin hydrochloride in *Medium* at the second time interval (mg/mL)
V = volume of *Medium*, 1000 mL
SV_1 = volume of the sample withdrawn at 1 h (mL)
C_1 = content of metformin hydrochloride in *Medium* at 1 h (mg/mL)
L = label claim (mg/Tablet)